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Review Article

COMPARATIVE MIC PROFILING OF COLISTIN AND POLYMYXIN B REVEALS SPECIES-SPECIFIC SUSCEPTIBILITY AND DILUTION DISCORDANCE AMONG GRAM-NEGATIVE BACTERIA.

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Abstract
Resistance in Gram-negative bacteria has increased dependence on last-line drugs like colistin and polymyxin B, but their minimum inhibitory concentration (MIC) may differ across species. This study compared species-specific colistin and polymyxin B MIC profiles and quantified paired dilution agreement and discordance among Gram-negative bacterial isolates. A total of 160 isolates of Klebsiella pneumoniae, Escherichia coli, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp. were included in the retrospective quantitative study. Medians, IQR's, MIC50 and MIC90 were used to characterize MIC distributions, and non-parametric tests were used to test species differences, paired MIC differences and correlations. Overall MIC50/MIC90 values were 0.25/16 for colistin and 0.125/0.5 for polymyxin B. Colistin MICs differed significantly across species ($H = 9.346$, $p = 0.025$), whereas polymyxin B MICs did not ($p = 0.434$). Paired MICs differed significantly ($W = 67.5$, $p < 0.001$; $r = 0.838$) and showed a moderate positive correlation ($\rho = 0.580$, $p < 0.001$). Agreement was 65.6% within ±1 dilution and 77.5% within ±2 dilutions, while 22.5% of pairs differed by more than two dilution steps. These findings demonstrate related but non-equivalent MIC patterns, supporting organism-specific interpretation of colistin and polymyxin B susceptibility.

Key Words: colistin, polymyxin B, minimum inhibitory concentration, Gram-negative bacteria, dilution discordance

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1. Introduction

The problem of antimicrobial resistance (AMR) is a significant challenge in the management of bacterial infections, making it difficult to achieve the desired outcomes of therapy, to avoid hospitalization, and to avoid complications. Gram-negative bacteria are especially challenging to treat due to the thick outer membrane, efflux mechanisms and ability to acquire multiple resistance determinants. This ongoing emergence of resistance has thus put strain on antimicrobial stewardship and the remaining effective antimicrobial treatment options (Morrison & Zembower, 2020). The clinical implications are especially concerning in susceptible populations, in which infections with antimicrobial-resistant Gram-negative bacteria can rapidly advance, and limited treatment options are available (Folgori et al., 2017). Resistant Gram-negative infections need careful consideration of the organism, the resistance phenotype, site of infection and the available active antimicrobials. The complexity of antibiotic resistance and the treatment of infections with resistant P. aeruginosa, A. baumannii, and Enterobacterales are reflected in the contemporary clinical guidance (Tamma et al., 2024). Additionally, resistant bacterial infections continue to be a significant issue among hospitalized patients and are a source of considerable difficult-to-treat disease (Wolford et al., 2025). The impact is not limited to specific individuals, as AMR imposes an extra burden on healthcare resources and poses a risk to achieving global public health and sustainable development targets (Aslam et al., 2024).

A number of Gram-negative organisms are at the heart of this issue. Infection with K. pneumoniae is a significant therapeutic and infection control problem due to the fact that resistance may occur to a number of antimicrobial classes (Bassetti et al., 2018). Multidrug resistance (MDR) reduces the therapeutic options for Acinetobacter baumannii, an important pathogen of hospital-acquired infections (Ibrahim et al., 2021). Resistant P. aeruginosa poses similar challenges, as it can inhibit many treatment options due to its intrinsic and acquired resistance (Kunz Coyne et al., 2022). The challenges have kept up interest in antimicrobials active against resistant Gram-negative bacteria. The role of the polymyxins in this context is of importance, since their antibacterial action is based on engagement of lipopolysaccharide and disruption of the outer membrane of the Gram-negative bacteria. They have also demonstrated targeting ability to the membrane, which has enabled further studies of polymyxin use in resistant organisms (Vaara, 2019). Members of this antimicrobial class are closely related with regard to activity against Gram-negative species, and it is important to have accurate characterization of their minimum inhibitory concentration (MIC) when evaluating activity across the Gram-negative species, especially when evaluating colistin and polymyxin B.

Several mechanisms of bacterial resistance, including lipid A modification and other changes that alter the interaction of the antimicrobial with the outer membrane, affect the susceptibility of bacteria to colistin. A variety of mechanisms can be responsible for reduced colistin susceptibility, as has been shown in Escherichia coli research, which has seen significant variation in MIC distributions between isolates of the same or different species (Abavisani et al., 2023). Polymyxins have biological heterogeneity, and quantitative MIC profiling can be relevant when investigating their activity. In addition to these challenges, laboratory testing of colistin susceptibility is also complicated. There have been discrepancies between phenotypic assays, and between phenotypic and underlying genomic resistance mechanisms for colistin (Torres et al., 2021). The interpretation of the MIC should, as such, not be taken for granted and should be interpreted with caution, especially when comparing different microorganisms or closely related antimicrobial agents. Broadly speaking, the polymyxin literature suggests that species and acquired/chromosomal resistance determinants both influence the antibiotic activity and resistance to polymyxins. Susceptibility testing is particularly relevant due to the existence of several mechanisms by which polymyxins can become resistant, including transferable determinants that have the ability to change the susceptibility profile (Poirel et al., 2017). Colistin and polymyxin B are from the same antimicrobial class, but the MIC data cannot be assumed to be numerically equivalent between bacterial isolates. The information obtained in direct paired analysis can then be different from what can be obtained via susceptibility summaries.

The current studies have provided clear evidence of the clinical importance of polymyxins, mechanisms of colistin resistance and difficulties with susceptibility testing. There has been less focus on isolate-level comparison of colistin and polymyxin B MICs across several clinically relevant Gram-negative pathogens using paired measurements. Little evidence is, however, available on the extent of the difference or equality of paired MIC measurements by one or more two-fold dilution step. There is also not enough information on how this discordance varies between species. An integrated assessment of MIC50 and MIC90 profiles, MIC relationships for two polymyxins, dilution level agreement and interspecies differences can give a more accurate picture of the similarities and differences between these two polymyxins.

The objectives were to characterize colistin and polymyxin B MIC profiles among Gram-negative bacteria, assess paired MIC relationships, quantify agreement and discordance in two-fold dilution steps, and determine whether MIC profiles and dilution differences varied among bacterial species.

2. Methodology

2.1 Research Design

A retrospective quantitative microbiological study was carried out to compare the minimum inhibitory concentration (MIC) profile of colistin and polymyxin B in Gram-negative bacterial isolates. A total of 160 isolates of Klebsiella pneumoniae, Escherichia coli, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp. were analyzed. Organism-specific MIC patterns, paired MIC differences and dilution agreement were tested.

2.2 Data Source

Microbiological data were extracted from a public repository of research (Radhakrishnan, 2024). The data included information about the bacterial organism identified as well as simultaneous colistin and polymyxin B MIC values. The records were analysed comparatively and on a species basis.

2.3 Data Preparation and MIC Processing

Records were scanned for missing data and for duplication of data, and bacterial nomenclature standardized. The forms in which entries were reported for the MICs were kept as reported but converted to numerical values. "≤" values were reported as the corresponding concentration, while the one reported colistin value >256 was used as 512 for numerical analysis. Separate data on censoring status were maintained.

2.4 MIC Profiling

The frequencies and percentages of bacterial isolates were presented. The median, interquartile range (IQR), MIC50 and MIC90 were calculated and used to describe colistin and polymyxin B MIC profiles, along with the MIC range reported. These measures were computed for each organism and overall. A base-2 scale was used to visualize MIC distributions.

2.5 Paired MIC and Dilution Agreement

The MIC of colistin and polymyxin B was compared for each isolate. Dilution differences were obtained as the difference in paired concentrations, expressed as a base-2 log difference. Agreement was defined as identical MIC, within ±1 dilution, within ±2 dilutions or more than two dilutions apart. The direction of the difference was also noted as to which of the two antimicrobials had the higher numerical MIC.

2.6 Statistical Analysis

Non-parametric tests were used for statistical analyses as they are suitable for the MIC distributions. The Kruskal–Wallis test was used to test for species-level differences, using epsilon-squared (ε^2) as a measure of the effect size. The species-level inferential analysis was not performed for Enterobacter spp. due to the small sample size (n = 2). Significant omnibus

tests were followed by Holm-adjusted Dunn tests. The colistin and polymyxin B MICs were compared in pairs using the Wilcoxon signed-rank test and the results interpreted in terms of effect size (r). The correlation between their association was evaluated via Spearman rank correlation (ρ). Species differences in paired dilution values were compared by the Kruskal–Wallis test and Dunn comparisons (when applicable) with Holm adjustment of the p-values. All tests were two-tailed; $p < 0.05$ was significant.

3. Results

3.1 Distribution of Bacterial Isolates

160 Gram-negative bacterial isolates were used in the analysis. The most common organism was Klebsiella pneumoniae (54 cases, 33.8 %), followed by Escherichia coli (52 cases, 32.5 %), Acinetobacter baumannii (33 cases, 20.6 %) and Pseudomonas aeruginosa (19 cases, 11.9 %). Two isolates (1.2%) were Enterobacter spp. The distribution of the bacterial isolates studied is given in Table 1. Figure 1 depicts the relative frequencies of the five groups of bacteria, with K. pneumoniae and E. coli being the highest.

Table 1. Distribution of Gram-Negative Bacterial Isolates

Bacterial organism	n	Percentage (%)
Klebsiella pneumoniae	54	33.8
Escherichia coli	52	32.5
Acinetobacter baumannii	33	20.6
Pseudomonas aeruginosa	19	11.9
Enterobacter spp.	2	1.2
Total	160	100.0

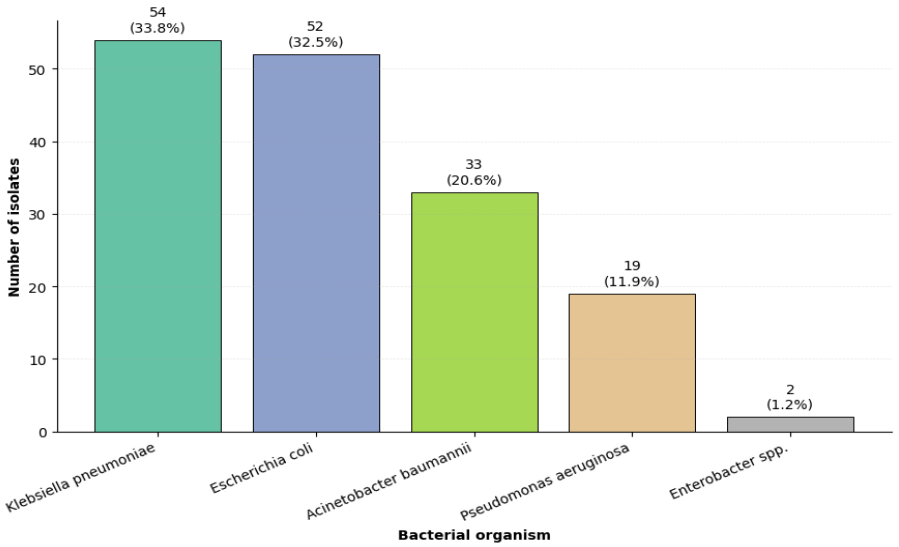

Figure 1. Distribution of Gram-negative bacterial isolates included in the study.

3.2 Colistin and Polymyxin B MIC Profiles

The MIC distributions differed for each bacterial organism and for each of the two antimicrobials. The median MIC values were 0.25 for K. pneumoniae, 0.125 for E. coli, 0.25 for A. baumannii and 0.5 for P. aeruginosa for colistin. The corresponding MIC90 values were 16, 2, 4 and 8, respectively. The median MIC was 0.125 for all four species, and MIC90s were 1, 0.25, 0.5, and 0.25, respectively. The summary of the MICs for both antimicrobials by species is presented in Table 2.

Table 2. Colistin and Polymyxin B MIC Profiles by Bacterial Organism

Bacterial organism	Antimicrobial	n	Median MIC (IQR)	MIC50	MIC90	Reported MIC range
Klebsiella pneumoniae	Colistin	54	0.25 (0.125–1.75)	0.25	16	≤0.125 to >256
Klebsiella pneumoniae	Polymyxin B	54	0.125 (0.125–0.125)	0.125	1	≤0.125 to 8
Escherichia coli	Colistin	52	0.125 (0.125–0.25)	0.125	2	≤0.125 to 256
Escherichia coli	Polymyxin B	52	0.125 (0.125–0.125)	0.125	0.25	≤0.125 to 16
Acinetobacter baumannii	Colistin	33	0.25 (0.125–0.5)	0.25	4	≤0.125 to 256
Acinetobacter baumannii	Polymyxin B	33	0.125 (0.125–0.125)	0.125	0.5	≤0.125 to 32
Pseudomonas aeruginosa	Colistin	19	0.5 (0.125–2)	0.5	8	≤0.125 to 64
Pseudomonas aeruginosa	Polymyxin B	19	0.125 (0.125–0.125)	0.125	0.25	≤0.125 to 0.25
Enterobacter spp.	Colistin	2	128 (128–128)	128	128	128 to 128
Enterobacter spp.	Polymyxin B	2	4 (4–4)	4	4	4 to 4

The species-specific colistin MIC distribution is presented with a broader range of values for the 4 main groups of bacteria as shown in Figure 2A. The polymyxin B MIC distributions shown in Figure 2B are similar, with most of the MICs at the lower levels.

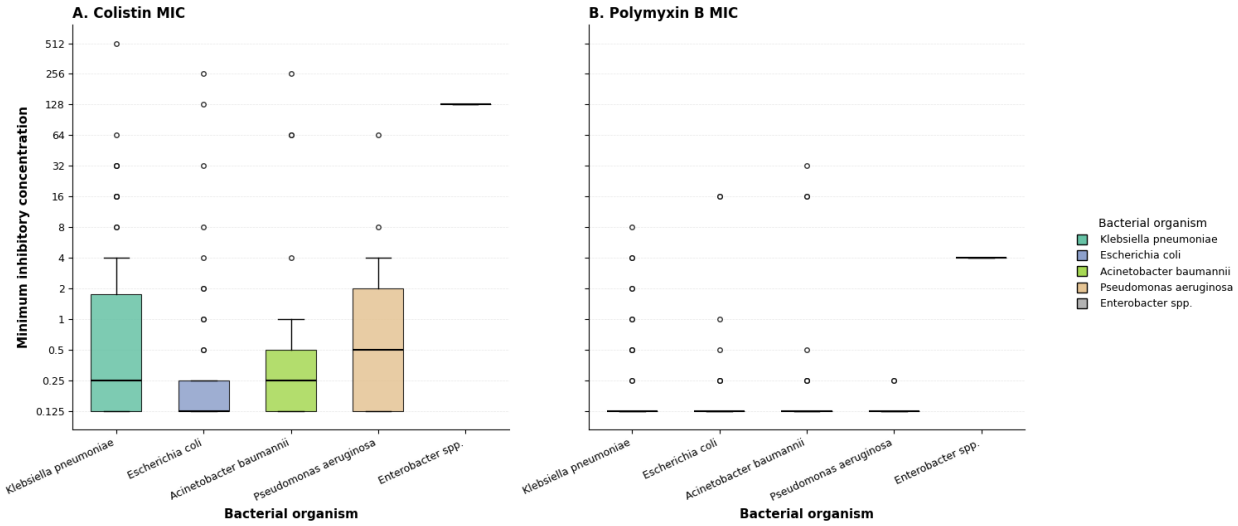

Figure 2. Species-specific distributions of colistin and polymyxin B minimum inhibitory concentrations among Gram-negative bacterial isolates. (A) Colistin MIC distribution. (B) Polymyxin B MIC distribution.

3.3 Statistical Comparison of MIC Patterns

A total of 158 isolates of K. pneumoniae, E. coli, A. baumannii and P. aeruginosa were included in the species-level inferential analyses. Colistin MIC varied significantly between the species ($H = 9.346$, $df = 3$, $p = 0.025$) and the epsilon-squared value was 0.041. No further pairwise comparisons were significant after Holm adjustment, however. There was no statistically significant difference in the Polymyxin B MIC among species ($H = 2.737$, $df = 3$, $p = 0.434$). The paired comparisons of colistin MICs versus polymyxin B MICs were significant ($W = 67.5$, $p < 0.001$; $r = 0.838$). Both measurements of MIC were also significant (Spearman $\rho = 0.580$ and $p < 0.001$). Paired dilution differences varied significantly among the four species ($H = 11.146$, $df = 3$, $p = 0.011$; $\varepsilon^2 = 0.053$). Table 3 shows the results of the

inferential statistical analyses. The correlation between colistin and polymyxin B MIC is presented in Figure 3 (Spearman $\rho = 0.580$, $p < 0.001$). The dashed diagonal represents numerical equality between paired colistin and polymyxin B MIC values.

Table 3. Inferential Statistical Analysis of Colistin and Polymyxin B MIC Patterns

Analysis	Statistical test	N	Statistic	df	p-value	Effect size
Colistin MIC across bacterial species	Kruskal–Wallis	158	H = 9.346	3	0.025	ε^2 = 0.041
Polymyxin B MIC across bacterial species	Kruskal–Wallis	158	H = 2.737	3	0.434	ε^2 = 0.000
Paired colistin vs polymyxin B MIC	Wilcoxon signed-rank	160	W = 67.5	—	<0.001	r = 0.838
Association between paired MIC measurements	Spearman rank correlation	160	$\rho = 0.580$	—	<0.001	—
Paired dilution difference across bacterial species	Kruskal–Wallis	158	H = 11.146	3	0.011	ε^2 = 0.053

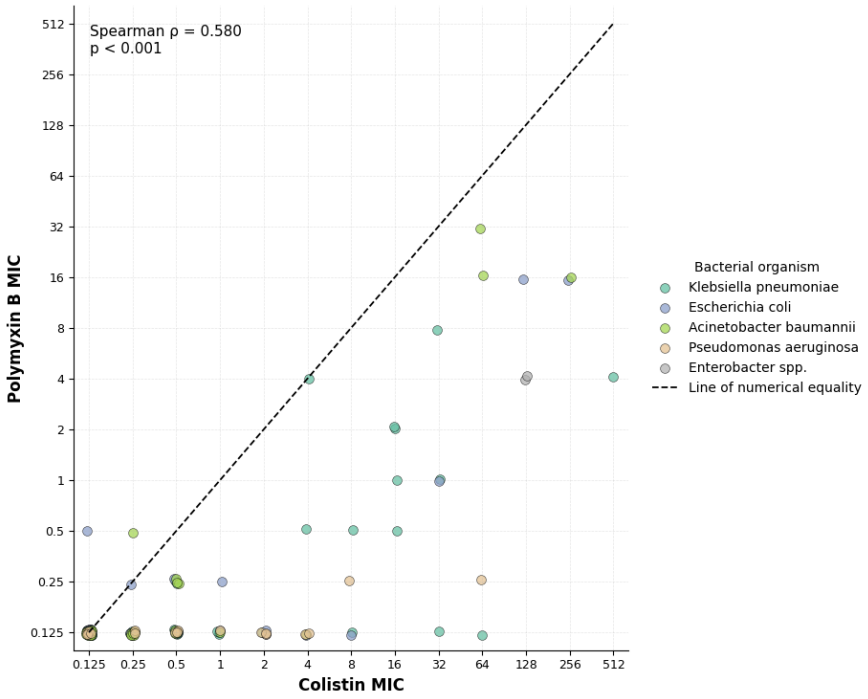

Figure 3. Relationship between paired colistin and polymyxin B minimum inhibitory concentrations among Gram-negative bacterial isolates.

3.4 Paired MIC Agreement

The 160 paired measurements showed 73 identical numbers in terms of their MIC (45.6%). A total of 105 pairs (65.6%) were within ±1 two-fold dilution, and 124 (77.5%) were within ±2 two-fold dilutions. There were differences that were more than two dilution steps in 36 isolates (22.5%). The MICs of colistin and polymyxin B differed numerically in 85 isolates (53.1%) and in two isolates (1.2%) with higher MICs for colistin and polymyxin B, respectively. The overall paired agreement and direction of the differences observed are presented in Table 4.

Table 4. Overall Paired MIC Agreement and Directional Differences

Measure	Overall, n (%)
Identical numerical MIC	73 (45.6%)
Within ±1 two-fold dilution	105 (65.6%)
Within ±2 two-fold dilutions	124 (77.5%)

Difference >2 two-fold dilutions	36 (22.5%)
Colistin MIC numerically higher	85 (53.1%)
Polymyxin B MIC numerically higher	2 (1.2%)

3.5 Species-Specific Dilution Agreement

The level of agreement was different among the bacterial groups. 61.5% of E. coli isolates, 42.6% of K. pneumoniae, 36.4% of A. baumannii and 31.6% of P. aeruginosa isolates were found to have identical MICs. Agreement within ±1 dilution was 78.8%, 57.4%, 75.8%, and 42.1%, respectively. The corresponding proportions within ±2 dilutions were 84.6%, 72.2%, 90.9%, and 57.9%. Median paired dilution differences were 0 for E. coli, 1 for A. baumannii and K. pneumoniae, and 2 for P. aeruginosa. The differences were >2 steps of dilution in 9.1% of A. baumannii, 15.4% of E. coli, 27.8% of K. pneumoniae, and 42.1% of P. aeruginosa. Table 5 shows the species-specific paired MIC dilution agreement.

Table 5. Species-Specific Paired MIC Dilution Agreement

Bacterial organism	N	Median dilution difference	Identical MIC, n (%)	Within ±1 dilution, n (%)	Within ±2 dilutions, n (%)	>2 dilutions apart, n (%)
Acinetobacter baumannii	33	1.0	12 (36.4%)	25 (75.8%)	30 (90.9%)	3 (9.1%)
Enterobacter spp.	2	5.0	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)
Escherichia coli	52	0.0	32 (61.5%)	41 (78.8%)	44 (84.6%)	8 (15.4%)
Klebsiella pneumoniae	54	1.0	23 (42.6%)	31 (57.4%)	39 (72.2%)	15 (27.8%)
Pseudomonas aeruginosa	19	2.0	6 (31.6%)	8 (42.1%)	11 (57.9%)	8 (42.1%)

Inferential testing was performed on the four species included, with the Dunn post-hoc analysis showing one significant difference between paired dilutions (Holm-adjusted $p = 0.0162$) between E. coli and P. aeruginosa. There were no other pairwise comparisons that were significant after Holm adjustment.

4. Discussion

The MIC profile comparison revealed quantitative differences between colistin and polymyxin B for all of the Gram-negative isolates. Colistin had a wider range of MICs and a higher MIC90, while the MICs of polymyxin B were grouped closer to the lower end of the dilution range. Overall, the MIC50/MIC90 values for colistin and polymyxin B were 0.25/16 and 0.125/0.5, respectively, signifying a high degree of variability in colistin MICs. Species-level analysis showed a significant overall difference in colistin MICs across the four major species, although the effect size was small and no individual pairwise comparison remained significant after Holm adjustment. There was very little variation in polymyxin B MICs between species. The paired analysis was able to give a clearer-cut separation between the two antimicrobials. The paired MICs differed significantly and showed a large matched-pairs effect size, while the moderate positive Spearman correlation indicated that isolates with relatively higher MICs to one polymyxin tended to have higher MICs to the other. Despite this positive association, the paired MIC measurements were not consistently numerically equivalent. Only 45.6% of the paired measurements matched, 65.6% of the pairs differed by no more than one two-fold dilution, and 77.5% differed by no more than two two-fold dilutions. Overall, 22.5% of paired measurements differed by more than two dilution steps; colistin MIC was numerically higher in 53.1% of isolates, whereas polymyxin B MIC was higher in only 1.2%. Further species-specific dilution analysis revealed heterogeneity. E. coli

showed the highest proportion of identical paired MICs (61.5%), whereas P. aeruginosa showed the lowest among the four major species (31.6%) and had the largest median paired dilution difference of two steps. P. aeruginosa also had the highest proportion of measurements more than two dilutions apart (42.1%). The overall species effect on paired dilution differences was significant, with the Holm-adjusted post-hoc analysis identifying a significant difference between E. coli and P. aeruginosa.

The difference in colistin and polymyxin B MIC observed is consistent with previous studies showing that colistin and polymyxin B are not necessarily microbiologically interchangeable within the same class of antimicrobials. Huang et al. (2025) directly compared the MICs of colistin and polymyxin B for Enterobacterales, A. baumannii and P. aeruginosa, thus emphasizing the need for organism-specific comparative assessment. Pharmacokinetic/pharmacodynamic modelling of polymyxin B has also highlighted that the MIC is pivotal to establishing clinically relevant targets for exposure and susceptibility thresholds (Bian et al., 2022). The other feature of this colistin coverage is that resistance to this last-line defence drug was broadly distributed, consistent with historical concerns about detection and interpretation of resistance to last-line drugs from Gram-negative organisms. Small differences in the laboratory susceptibility profile may make recognition of resistance difficult, especially when a small difference in the MIC is used to make a difference between susceptibility and resistance (Sherry & Howden, 2018). The discordant paired MICs found in the present analysis have been microbiologically supported, as polymyxin B and colistin have been shown to differ in measured activity against MDREs in previous comparative testing of these two antimicrobial agents against Gram-negative bacteria (Doymaz & Karaaslan, 2019). In addition, clinical literature also suggests that there are other differences between the two polymyxins beyond the lab results for MIC. While universal equivalence of colistin and polymyxin B has not been established, comparative evidence has evaluated both drugs in terms of treatment outcomes and toxicity in the treatment of multidrug-resistant Gram-negative infections (Vardakas & Falagas, 2017).

Clinical comparisons have also identified differences in effectiveness and adverse-effect profiles between colistin and polymyxin B, further supporting careful distinction between the two agents (Simon et al., 2023). Despite the relatively low polymyxin B MICs recorded for various organisms, this is consistent with reports of microbiological activity of polymyxin B combinations against carbapenem-resistant Gram-negative infections (Qu et al., 2022). Biologically, there is also the possibility of species-specific variability since resistance to polymyxin can develop in several different ways within the genetic material. For some species, such as K. pneumoniae, resistance to polymyxins is broadly and also heterogeneously distributed, while for extensively drug-resistant K. pneumoniae, multifactorial variants in the chromosome have been identified to regulate polymyxin resistance, which may provide a mechanistic explanation for the widespread and more complex MIC distribution in these species (Pitt et al., 2018).

The results suggest that the Colistin and Polymyxin B MIC should be considered as different but related susceptibility parameters. Only reporting correlation would neglect the significant percentage of isolates with dilution level discordance. The use of MIC50, MIC90, paired dilution differences and organism-specific agreement gives a holistic view of polymyxin susceptibility. The species-dependent pattern also cautions for careful interpretation of the MIC results in P. aeruginosa and K. pneumoniae, where there were larger paired differences more frequently.

A few limitations should be considered. Only two Enterobacter spp. were recovered and were not sufficient to allow for reliable inferences at the species level. Lower limit censoring was common, especially for polymyxin B, which could have caused a loss of resolution for isolates with the lowest MICs. No clinical outcome or molecular resistance determinants were available, and the results are therefore only phenotypic. Larger species-specific sample sizes with colistin and polymyxin B MIC testing in pairs, along with clinical response data and resistance-genotype data, should be used in future studies to better understand the biological and clinical implications of dilution discordance.

5. Conclusion

Comparative MIC profiling revealed that colistin and polymyxin B are closely related polymyxins, but have not been completely numerically equivalent in Gram-negative bacterial isolates. Colistin had a wider distribution of MICs and higher MIC90s, and polymyxin B had more MICs at lower dilutions. Although there were moderate positive correlations in the ranking of the MICs, paired analysis revealed there was a significant difference between the two agents. Agreement was not complete, with 65.6% of isolates being within ±1 two-fold dilution, 77.5% within ±2 dilutions and 22.5% more than two steps away. Further analysis of the species-specific patterns indicated that there was no uniformity in the extent of dilution discordance, with the paired separation of Pseudomonas aeruginosa species being greater than that of Escherichia coli species. These results may aid organism-specific interpretation of polymyxin MIC results and warn against using colistin and polymyxin B measurements as interchangeable. Larger species-specific samples and molecular resistance data combined with clinical outcome data could be used in future studies to elucidate the biological and therapeutic implications of the observed discordance in MICs.

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